IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 99-849-A)

In the Application of:	)	
	)	
Odile Leroy	)	
	)	**Examiner: Duffy, P.A.**
Serial No.: 09/423,698	)	
	)	**Group Art Unit: 1645**
Filing Date: February 10, 2000	)	
	)	**Confirmation No.: 7060**
For: Multivalent Vaccine Composition With Mixed Carrier	)	

RULE 132 DECLARATION OF DOMINIQUE SCHULZ

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Dominique Schulz, declare as follows:

1. I am currently employed by Sanofi Pasteur SA, which, on information and belief, is the assignee of this patent application.

2. I have a degree in Biochemistry (A.E.A.) from the University of Lyon I. Since 1991 I have had responsibilities within the Research & Development Department of Sanofi Pasteur (in 1997, the company was called Pasteur Mérieux sérums & vaccins). I was Project Leader of the pneumococcal glycoconjugate vaccine project (pneumo vaccine) from 1991 to 1999, and then Deputy Project Leader from 2000 to 2002, the year the project ended.

3. I am therefore completely familiar with the technology that is the subject of U.S. patent application no. 09/423,698 as well as with the competitor pneumococcal glycoconjugate vaccines that were developed in the nineties. In particular, I have closely interacted with the inventor cited in the present application (Dr Odile Leroy who was the clinical team

leader) and was deeply involved in the relationship with the external clinical investigators of the vaccine, Drs Juhani Eskola and Ron Dagan.

4. On information and belief, I understand that the issues being considered with respect to this patent application by the U.S. Patent Office involve, among other things, the knowledge, understanding, and skill level of a person of ordinary skill in the art pertaining to the claimed vaccine composition in the 1997 time-frame. I have been asked to submit this Declaration to address these matters. I believe I am qualified to address these matters because of the relevant educational and work experience set forth in paragraphs 2 and 3 above.

5. I have read and understand the contents of this patent application (*i.e.*, U.S. patent application no. 09/423,698) and the claims that, on information and belief, are being submitted concurrently with this Declaration. A copy of these claims is presented in Appendix A of this Declaration.

6. The claims are directed to a multivalent glycoconjugate combination vaccine against *Streptococcus pneumoniae* infections, which comprises at least two protein carriers that include Tt and Dt. As noted on p. 2 of the specification, the need for *Streptococcus pneumoniae* vaccines is particularly high among young children, and the presently claimed composition can be used to immunize children, including, for example infants (*e.g.*, breast-feeding infants (specification p. 6, l. 35 *et seq.*)). Furthermore, it is my belief that those working in the field of developing *Streptococcus pneumoniae* glycoconjugate vaccines in 1997 would understand that the primary use of the claimed vaccine would have been pediatric.

7. On information and belief, I understand that Odile Leroy, the inventor of this patent application, had MD and MPH (Master in Public Health) degrees with post-doctoral experience and more than five years of work experience developing vaccines in the vaccine industry. As mentioned above, she was the clinical team leader of the pneumo vaccine team acting under my management at Pasteur Mérieux sérums & vaccins (now called Sanofi Pasteur). She worked in a large network of people in the vaccine industry and, accordingly, would have been knowledgeable of the constraints (scientific, commercial, and regulatory) on vaccine development.

8. In view of the foregoing and in conjunction with my own educational and work experience in the field of vaccine development as well as the nature of the technology, my opinion is that the person of ordinary skill in the art pertaining to development of new *Streptococcus pneumoniae* vaccines (such as those claimed in Appendix A) was someone with training and experience comparable to Dr. Leroy's and who was concerned with the development and commercial scale production of such vaccines.

9. Such a person would possess and be influenced by knowledge and factors specific to the vaccine developers in addition to those of an academic researcher concerned solely with fundamental scientific inquiry. Furthermore, because of the practical nature of the task of vaccine development, the person of ordinary skill in the art would have been guided primarily by empirical evidence garnered from approved conjugate vaccines rather than theories or hypotheses concerning immunological mechanisms of action (although those would not be ignored). In addition, the person of ordinary skill in the art would be equally concerned with and influenced by regulatory matters generally affecting vaccine development.

10. Vaccines, like pharmaceuticals, can be marketed only after receiving approval from governmental regulatory authorities. My understanding is that the regulatory requirements are even more demanding for vaccines than for conventional pharmaceuticals because vaccines are biological products that are administered to healthy people. An additional complication with regard to vaccines intended for pediatric use is that the they must be compatible with the other vaccines administered to children.

11. Clinical trials investigate the safety, appropriate dosage, administration schedule, efficacy and lot-to-lot consistency, of vaccines. Clinical data are key for gaining regulatory approval. However, tests and data other than clinical are also required by regulatory authorities. In particular, regulatory authorities ask for extensive characterization of each vaccine component. Increasing the number of components increases the number of assays that must be developed, validated, and performed on both the individual components and the combination vaccine. Each of these assays must give satisfactory results, and the more of these there are, the greater the expense, the longer the development time, and the more variables there are to go wrong. This means, in particular, that the addition of a

particular, that the addition of a component must be fully justified first in terms of public health needs and then in terms of costs to warrant the increased complexity. Accordingly, there must be clear, persuasive, and well-defined reasons for including each component into a vaccine composition.

12. As a general manner, one of ordinary skill in the art of developing *Streptococcus pneumoniae* conjugate vaccines would have been cognizant of the scientific hurdles that could be encountered in developing a new vaccine. However, as they essentially occur on an unpredictable basis, he would not have been in a position to anticipate any detrimental effect resulting from, for example, the combination of several components. Indeed, owing to the complexity of the immune system, vaccine development was and continues to be largely an empirical process. Generally, the art has progressed incrementally on the basis of such experience.

13. In view of the issues discussed in paragraphs 9 through 12, my opinion is that one of the ordinary skill in the art of developing *Streptococcus pneumoniae* conjugate vaccines in 1997 would have proceeded very cautiously in formulating a new vaccine, considering very carefully each component and ensuring the reasons justifying its inclusion were sufficiently great to outweigh the development efforts that would be necessitated by its inclusion. The consequences of error can be serious both from a clinical and commercial perspective and are only heightened upon the realization that *Streptococcus pneumoniae* vaccines such as presently claimed are for pediatric use, *i.e.*, for administration to healthy infants. Another reason for proceeding cautiously lies within the fact that animal models are not predictive for *Streptococcus pneumoniae* infections. Most of the development must therefore be conducted in humans. As a result of all of the foregoing as well as the time and costs involved, the approach adopted by one of ordinary skill in the art would be a cautious and conservative one.

14. Accordingly, vaccine developers in 1997 generally followed two fundamental principles: (a) follow proven vaccine development strategies if at all possible; and (b) keep the formulation as simple as possible (*i.e.*, use the fewest biological components for the vaccine's intended purpose). Towards this end, vaccine developers in 1997 would generally have started with the lessons learned from vaccines with a proven track record

(*i.e.* those that had been approved, were on the market, and were successful). This is especially true in the field of glycoconjugate vaccines given the relatively few that were approved at the time of the present invention.

15. Polysaccharides are T-independent antigens *i.e.* they are unable to induce an immune response in infants of less than 2 years of age. The general concept of conjugating a T-independent antigen to a protein carrier for inducing an immune response against the T-independent antigen was known and first reduced to practice in animals in 1929. But nearly 60 years lapsed before the first glycoconjugate vaccine was approved in 1987 for 18-month to 5-year old children [ProHIBiT™, a Hib conjugate (PRP-Dt)]. By 1997, all the licensed glycoconjugate vaccines of which I am aware, were anti-*Haemophilus influenzae type b* (Hib vaccines), with only three additional Hib glycoconjugate vaccines having been approved since 1990 for infants over 2 months of age (HibTITER™, PedVax Hib™ and Act-HIB™ (PRP-Tt)). Prevnar™, a seven-valent glycoconjugate vaccine against *Streptococcus pneumoniae* using CRM197 as the sole carrier, was the first licensed pneumococcal glycoconjugate vaccine. But it was not approved in the USA until 2000. As far as I am aware, no *Streptococcus pneumoniae* glycoconjugate vaccine was licensed in 1997.

16. As noted on page 2 of the specification, there are a number of *Streptococcus pneumoniae* serogroups/serotypes that are not immunologically cross-reactive. Consequently, *Streptococcus pneumoniae* vaccine developers in 1997 were pursuing vaccines comprising multiple *Streptococcus pneumoniae* polysaccharides from a variety of serogroups/serotypes for inducing broad spectrum immunity. In 1977, following renewed interest in prophylactic immunization, a 14-valent (14 capsular polysaccharides) pneumococcal polysaccharide vaccine containing 50 μg of each capsular polysaccharide received marketing approval for administration to adults. This was followed by a 23-valent pneumococcal polysaccharide vaccine using half the amount of each capsular polysaccharide (25 μg) in 1983. By May 1997, three 23-valent pneumococcal polysaccharide vaccines were on the market: Pneumovax 23 (Merck, Sharp & Dohme); Pnu-Immune 23 (Wyeth-Lederle Vaccines); and Pneumo 23 (Pasteur Mérieux

Connaught). But as noted in the previous paragraph, in 1997 there were no *Streptococcus pneumoniae* glycoconjugate vaccines on the market.

17. For developing an improved pneumococcal glycoconjugate vaccine including at least 10 valencies (such as in the appended claims), my view is that a vaccine developer in 1997 would have undertaken to build on proven success and, accordingly, looked closely to licensed vaccines. Consequently, were a vaccine developer to decide on employing glycoconjugates, once a particular carrier protein/conjugation strategy had been proven to be safe and immunogenic in the target population and received regulatory approval, one of ordinary skill in the art would have sought to stick with it and not change strategy absent a very strong and well defined motivation to do so. Thus, in my view, one of ordinary skill in the art would have turned his attention to the Hib glycoconjugate vaccines described in paragraph 15 above, which were the only glycoconjugate vaccines on the market and which all employed only a single protein carrier.

18. I was not aware in 1997 and am still not aware of any multivalent glycoconjugate vaccine being developed at that time employing more than one protein carrier. The unprecedented use of more than one protein carrier when a single carrier may have sufficed to achieve efficacy when

    (a) there were no well-defined and convincing reasons for employing more than one carrier protein and

    (b) there were no contra-indications for use of a single carrier,

would have been, in my view, a strategy inconsistent with general practice of those of ordinary skill in the art at the time of the invention and the additional reasons described above. Rather, one of ordinary skill in the art would have been motivated to use a single carrier for the synthesis of each monovalent glycoconjugate component because it would have simplified the manufacturing and regulatory aspects of vaccine development, thereby saving time and costs and reducing the unpredictability of the entire process.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 16, 2016

Dominique Schulz

APPENDIX A

Listing of Claims:

1. (Currently Amended) A vaccine composition comprising a dose of "n" conjugates C1 to Cn, wherein
   (a) each conjugate comprises
      (i) a polysaccharide S1 to Sn from a *Streptococcus pneumoniae* serotype/serogroup, respectively, and
      (ii) a carrier protein P1 to Pn, respectively;
   (b) "n" is a number equal to or greater than 10;
   (c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and
   (d) the carrier proteins P1 to Pn are selected independently from a group consisting of "m" carrier proteins, wherein "m" is a number equal to or greater than 2;
   (e) at least one of P1 to Pn is Dt and at least one of P1 to Pn is Tt; and
   (f) the amount of conjugated Dt protein is less than or equal to 60 μg/dose and the amount of conjugated Tt protein in the composition is less than or equal to 25 μg/dose.

2. (Previously presented) The composition according to Claim 1, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

3. (Previously presented) The composition according to Claim 2, in which the polysaccharides S1 to Sn are all different from each other.

4. (Canceled)

5. (Canceled)

6. (Previously presented) The composition according to Claim 1 in which the carrier proteins P1 and Pn are independently selected from Dt and Tt.

7. (Previously amended) The composition according to Claim 6, in which when "n" is an even number, "n"/2 carrier proteins P1 to Pn are a first protein and "n"/2 carrier proteins

P1 to Pn are a second protein or when "n" is an odd number, ("n"+1)/2 carrier proteins P1 to Pn are a first protein and ("n"-1)/2 carrier proteins P1 to Pn are a second protein.

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Previously presented) The composition according to Claim 1, which comprises 10 or 11 conjugates in which the polysaccharides S1 to Sn are all different from each other and are chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F of *S. pneumoniae*.

13. (Previously presented) The composition according to Claim 12, which comprises 10 or 11 conjugates selected from:
- serotype 1 polysaccharide coupled to Tt or to Dt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt or to Dt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 7F polysaccharide coupled to Tt or to Dt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 19F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Tt.

14. (Previously presented) The composition according to Claim 1 wherein n is 12 to 22 and the composition comprises 10 or 11 different polysaccharides S1 to Sn chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and in which conjugates having the same polysaccharide differ from each other in the carrier protein.

15. (Previously presented) The composition according to Claim 14, which comprises:
- serotype 1 polysaccharide coupled to Tt;

- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 6B polysaccharide coupled to Tt;
- serotype 7F polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Dt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Tt;
- serotype 19F polysaccharide coupled to Tt;
- serotype 23F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Dt.

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)